

Natural Rubber Latex Allergy

A Problem of Interdisciplinary Concern in Medicine

Randolf Brehler, MD; Birgitta Kütting, MD

In the past 10 years, IgE-mediated allergy to natural rubber latex has become a significant health problem in industrialized countries, especially among health care workers, patients with congenital malformations, and children with a history of multiple surgical interventions. Curative treatment inducing immunological tolerance in formerly sensitized patients is experimental and not yet generally available. Therefore, it is important to be aware of the seriousness of latex allergy and to understand the risk factors leading to this allergy. Preventive measures are needed to decrease the incidence of natural rubber latex sensitization. This article gives a brief review of the current state of knowledge concerning latex allergy, including a definition of *latex*, epidemiological data, identified allergens, the clinical spectrum, diagnostic procedures, cross-reactions, preventive measures, the legislative background, and economics.

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In today's health care practice, the use of gloves is indispensable. Because of their low price, high comfort, and tactile properties, natural rubber latex (NRL) gloves are preferred over synthetic ones. Contact dermatitis (allergic and nonallergic) is a well-known problem related to the use of NRL gloves, but during the last 20 years, the immediate reactions to NRL have been the focus. Between 1989 and 1992, the Food and Drug Administration received reports of more than 1000 serious allergic reactions and 15 deaths due to NRL allergy.¹

Immediate allergic reaction to NRL is a significant occupational problem for employees wearing NRL gloves; about 10% of health care workers are sensitized to NRL. On another level, patients are at risk of anaphylactic reactions due to contact with NRL during medical treatments, especially surgical procedures; about 19% of the anaphylactic reactions associated with anesthesia are caused by NRL allergy.² Gloves are not the sole source of contact with NRL in sensitized patients. Natural rubber latex is found in more than 40 000 medical devices and other nonmedical products (**Table 1**). To avoid exposure in daily life, sensitive patients must be able to identify products containing NRL, but the labeling of these products is not regulated in most countries.

Recent reviews³⁻¹³ focus on different aspects of NRL allergy, such as epidemiology, diagnostic procedures, allergen identification, prevention, and therapy, but despite the increasing awareness and prevention programs, NRL allergy is still a problem. Therefore, the current state of NRL allergy is examined in this review.

DEFINITION OF LATEX

To avoid confusion when discussing NRL allergy, clear definitions of the terms *latex* and *rubber* are needed because, depending on the context, they can have multiple meanings:

- *Natural rubber latex* refers to the milky sap produced by more than 2000 species of plants from about 300 genera.¹⁴ Industrial use of NRL is almost exclusively from the rubber tree *Hevea brasiliensis*.
- *Synthetic rubber* is produced by synthesis of polyisoprene or other polymers. The term *latex* is used in referring to NRL and synthetic rubber.
- A technical definition of *latex* is common in some countries, where the term refers to a suspension of different kinds of particles (such as latex wall paint) and does not necessarily indicate the presence of rubber latex in these products.

From the Department of Dermatology, University of Münster, Germany.

Table 1. Natural Rubber Latex in Medical and Privately Used Products

Medical Devices	Privately Used Products
Gloves	Balloons
Catheters	Condoms
Face masks	Clothes
Mattresses	Shoe soles
Stethoscope	Sport equipment
Blood tourniquets	Mattresses
Mouth sperrer	Glues
Rubber syringe	Pacifiers, feeding
stoppers	nipples
Medical vial	Toys
stoppers	

EPIDEMIOLOGY

Since the first epidemiological study among medical personnel by Turjanmaa,¹⁵ the prevalence of NRL allergy has increased. Today, between 10% and 17% of medical personnel in Europe and the US are believed to be sensitive to NRL.¹⁶⁻²⁶ Children with congenital malformations, especially those associated with spina bifida, are another well-identified risk group. The prevalence of NRL allergy in patients with spina bifida is about 50% in industrialized countries²⁷⁻³⁴ and about 5% in less industrialized countries, such as Venezuela.³⁵ This is believed to be related to contact with NRL during medical treatments, especially surgical interventions in early childhood. A history of multiple surgical interventions has also been reported in the general population of children with sensitivity to NRL.³⁶ Sensitivity was found in 34.1% of children with a history of 3 or more interventions.³⁶ Surgical interventions are a risk factor for the development of NRL allergy in children^{28,34,36} but not in adults.³⁷

Higher prevalence of NRL allergy was also found among hairdressers,³⁸ housekeeping personnel,²⁴ latex doll manufacturers,³⁹ latex glove manufacturers,^{40,41} textile workers,⁴² and greenhouse workers.⁴³ The prevalence in the general population is unknown but has been estimated to be less than 1%.^{44,45}

CLINICAL REACTIONS

Clinical reactions to contact with latex gloves can be divided into 3

Table 2. Natural Rubber Latex (NRL) Glove-Related Skin Problems

Type of Reaction	Clinical Manifestation
Nonimmunological irritant contact dermatitis, due to occlusion, mechanical irritation, high glove pH, and sweat	Eczema predominantly on the back of the hands and fingers, with redness, infiltration, scaling, and fissures
T-cell mediated allergic contact eczema, mostly due to rubber chemicals, rarely due to NRL itself	Onset 24-48 h after contact. Acute allergic contact eczema, with redness, infiltration, vesicles and crusts, and itching By repeated contact, chronic allergic contact eczema; predominantly scaling, infiltration, lichenification Mostly located on the back of the hands and wrists
IgE-mediated immediate-type allergy, nearly exclusively due to NRL proteins, rarely due to casein, cornstarch, or rubber chemicals	Onset mostly within minutes, with localized erythema, itching, and contact urticaria Generalized urticaria, rhinitis, conjunctivitis, asthma, and anaphylactic shock

groups (**Table 2**): nonimmunological and delayed- and immediate-type allergy.

Nonimmunological irritant contact dermatitis is manifested as irritative eczema with redness, scaling, and itching, predominantly on the back of the hands and interphalangeal. In contrast to the others, this type of clinical reaction is not based on an immunological mechanism. It is a general problem of glove wearing that is independent of the chemical composition of the gloves. Gloves can induce skin irritation "mechanically" or by an alkaline pH:

- "Mechanical" irritation can be avoided by use of powder-free gloves. In tests of glove wearing on powdered vs unpowdered hands, laser profilometry demonstrated increased skin roughness after wearing the same glove on prepowdered hands.⁴⁶
- The alkaline pH of most powdered gloves is believed to be responsible for irritative skin reactions.⁴⁷ Powder-free gloves offer a lower surface pH that is in the range of normal skin pH. The presence of a long-lasting alkaline skin surface pH after removal of powdered gloves has been reported.⁴⁷

The second type of clinical reaction is manifested by a delayed-type allergic contact eczema caused by glove contact, usually on the back of the hands. Rubber chemicals, mostly accelerators, used for manufacturing latex products are responsible for such reactions.⁴⁸ Thiurams have been identified as the predominant contact sensitizers in NRL gloves. Because most manufacturers no longer use thiurams, the delayed-type reactions play a minor role.

Immediate-type reaction to NRL is IgE-mediated, and the term *latex allergy* is usually used to describe this. Localized itching, erythema, or contact urticaria within minutes after NRL exposure are initial symptoms. Progressive sensitization can also lead to generalized urticaria, angioedema, rhinitis, conjunctivitis, asthma, and anaphylactic shock minutes after dermal or mucosal contact with NRL proteins. An increasing number of individuals allergic to NRL report severe reactions to latex, including generalized urticaria, bronchospasm, and hypotension.⁴⁹

The severity of clinical reactions can be classified according to the system of von Krogh and Maibach.⁵⁰ Stage 1 of contact urticaria syndrome indicates localized urticaria; stage 2 denotes generalized urticaria with or without angioedema; stage 3 includes bronchial asthma, rhinoconjunctivitis, orolaryngeal, and gastrointestinal symptoms; and stage 4 is severe anaphylactic shock.

Glove powder is believed to play a central role in reactions to NRL products. Natural rubber latex proteins on gloves bind to the glove powder (usually cornstarch powder) and become aeroallergens. Therefore, respiratory tract reactions induced by aeroallergens may occur concomitantly with der-

dermal reactions caused by local dermal contact.^{51,52} In this case, a clear distinction between a systemic reaction produced by localized dermal contact and reactions caused by allergen inhalation is impossible. Parenteral latex exposure can also trigger reactions.^{53,54}

Because of resorption of NRL allergens through mucous membranes, NRL allergy is not only a problem for employees who wear latex gloves but also an increasing problem for sensitized patients undergoing medical treatment by persons wearing gloves. Fatal cases have been reported in the literature,^{2,31} especially during surgical interventions. About 19% of all anaphylactic reactions during surgery (anesthesia “accidents”) are related to NRL allergy,² and the percentage is higher in children.⁵⁵ The risk of anaphylaxis to NRL in children with spina bifida has been estimated to be 500 times greater than that in the general population.^{56,57}

ALLERGENS

Natural rubber latex derived from *H brasiliensis* contains more than 200 polypeptides, 56 of which have been identified as allergens associated with IgE-mediated reactions. Their molecular weight ranges from 4 to 200 kD. Some of the allergens have been characterized,⁵⁸⁻⁶¹ some as general major allergens and others as major allergens only for patients of defined risk groups. Hev b 1, for example, is a major allergen for children with spina bifida but not for health care workers.⁶²⁻⁶⁸ Different routes of NRL exposure and subsequent sensitization may explain this. Hev b 1 and Hev b 3, which are major allergens in children with congenital malformations, are particle-bound proteins and less soluble than other latex allergens, and sensitization to these allergens may result from repeated mucosal contacts.⁶⁵ It has been speculated that the aerogen NRL protein exposure associated with the use of powdered gloves in delivery rooms may be responsible for the development of NRL allergy in neonates.⁶⁹ Further variation has been identified in mice that have been subcutane-

ously sensitized to NRL, leading to the development of IgE antibodies recognizing 14-kD and 27-kD proteins. Intratracheally and topically sensitized animals produced IgE antibodies to 14-, 35-, and 92-kD proteins.⁷⁰

Some latex allergens are a part of a plant's defense system (Hev b 2 and class 1 endochitinases). This may explain the increasing prevalence of sensitivity to NRL. It is hypothesized that the amount of NRL obtained from an *H brasiliensis* tree increased in the last few years. There may be a correlation between the production of defense proteins in relation to the frequency and intensity of hurting the trees.⁵⁸

Further complicating the issue, Mäkinen-Kiljunen and colleagues⁵⁹ identified an allergen in a surgical glove extract that is not found in natural rubber, suggesting that rubber proteins may be altered during glove manufacture.

DIAGNOSIS

In Vitro

The quantitative measurement of serum-specific IgE antibodies to NRL is generally accepted as a diagnostic tool for latex allergy. However, the sensitivity of specific-IgE analysis ranges from 8% to 100%. For the widely used Pharmacia CAP (Pharmacia AB, Uppsala, Sweden) radioallergosorbent test method, the sensitivity is reported to range from 50% to 80%.⁷¹⁻⁷³ Data about the specificity of in vitro diagnosis are rare.^{71,74,75} Using different assay systems (CAP-FEIA [fluoroimmunoassay; Pharmacia AB] and AlaSTAT [Diagnostic Products Corp, Los Angeles, Calif]), NRL-specific IgE was detected in the serum samples of patients despite negative findings on skin tests and no history of NRL allergy.^{74,75} Cross-reacting IgE antibodies binding to plant proteins and NRL are believed to be responsible for this. Mäkinen-Kiljunen and Turjanmaa⁷⁴ found IgE specific to banana in the serum of most patients with a false-positive radioallergosorbent test for NRL. Also, IgE antibodies to *Ficus benjamina* (weeping fig) may account for the frequent false-positive finding of specific IgE

to NRL.⁷⁵ On the other hand, IgE antibodies against carbohydrates were shown to be the cause of IgE reactivity against a broad range of foods, from plant to invertebrate animal origin. These IgE antibodies have been shown to be responsible for positive results in in vitro-specific IgE assays, despite negative skin-prick test (SPT) results and an absence of clinically relevant sensitization.^{76,77}

In Vivo

Diagnosis of immediate-type NRL allergy should be based on positive SPT results. Because SPTs with single latex extracts have a sensitivity below 100%, it is necessary to use a panel of different allergen extracts.^{71,78-81} In Germany, extracts that are available from allergen manufacturers are generally unstandardized. High-ammoniated NRL milk, available from glove manufacturers, can be used exactly as received; glove extracts can be prepared by a short extraction in isotonic sodium chloride solution.^{82,83} Because of the potential risk for anaphylactic reactions associated with SPTs in patients allergic to NRL,^{30,81,84} it is recommended that diluted solutions be used initially. Recombinant NRL proteins can be used for SPTs, but a panel of allergens is necessary to get a sufficient sensitivity.⁸⁵

The reliability of NRL glove wearing test results depends on the test protocol and the protein concentration of the gloves used.⁸⁶ Increased sensitivity of exposure tests has been obtained by Hamilton and Adkinson⁸⁶ by puncturing the skin before contact with the NRL glove. A potential risk for anaphylaxis can be reduced by exposing only 1 finger to a glove finger before exposing the hand to the whole glove.⁵⁷

CROSS-REACTIVE ALLERGENS

Cross-reactions between proteins in NRL and several foods have been demonstrated, and a “latex-food” syndrome has been postulated.⁸⁷⁻⁸⁹ In one study, 43% of patients with NRL allergy reported reactions caused by the ingestion of foods, particularly tropical fruits. Fruit-specific IgE antibodies are present in about 70% of serum samples of pa-

tients allergic to NRL. However, their presence is of limited significance given the low sensitivity and specificity of *in vitro* tests relative to a patient's self-reported allergic reaction after fruit ingestion.⁸⁹ The relevance of fruit sensitization varies considerably, based on a patient's diet and cultural background. On Spain's Grand Canary island, sensitization to avocado was found to be the predominant food allergen in patients with latex allergy,^{87,90} whereas in Germany, reactions to kiwi, banana, and tomato were much more frequent.⁸⁹ Patatin,⁹¹⁻⁹⁴ profilin,^{95,96} chitinases,^{97,98} plant endo-1,3- β -glucosidases,⁹⁹ glucanases,^{99,94,99,100} and hevein¹⁰¹ are allergens believed to be responsible for cross-reactions.

Ortiz et al¹⁰² found IgE antibodies to NRL proteins in 85.9% of patients allergic to fruits. Only 10.5% of them had clinically relevant latex allergy. This indicates that patients sensitized primarily by food allergens may also react to NRL.

THERAPY AND PREVENTION

Desensitization

Several recent case reports¹⁰³⁻¹⁰⁶ of NRL-specific immunotherapy have been published. Administering oral¹⁰³ and subcutaneous¹⁰⁴⁻¹⁰⁶ allergens was demonstrated to be effective in reducing allergic symptoms from NRL contact; SPT sensitivity decreased during specific immunotherapy. In the first randomized, double-blind, placebo-controlled study¹⁰⁷ on 17 patients with NRL allergy, significantly lower rhinitis, conjunctivitis, and cutaneous scores were reported in the patient group, but asthma symptoms were not significantly different in patients vs controls. Therefore, NRL-specific immunotherapy remains an experimental treatment of NRL allergy, and avoidance of exposure remains the mainstay of therapy and prevention.

Protein Concentration of Gloves and Powder

The modified Lowry test is the current standard method for determination of protein content in gloves.¹⁰⁸ A protocol for protein analysis has

been issued by the European Union, but there are no guidelines about how many gloves from each batch need to be tested. Therefore, data from manufacturers can be based on the analysis of only a few gloves, with no guarantee that all the gloves, especially if they are from different batches, have the same protein content. Standardized protocols for the quantitative analysis of allergens in gloves are not available. A correlation between the protein concentration and the allergen concentration of gloves has been demonstrated by enzyme-linked immunosorbent assay and radioallergen sorbent test inhibition methods and SPT.¹⁰⁹

Significant variation in the NRL protein concentrations in different types of gloves has been observed by several investigators.^{49,109-112} Powder-free gloves normally have low protein concentrations because of special leaching procedures used in their production. The protein concentration of powdered gloves varies between 45 and 1640 $\mu\text{g/g}$.¹⁰⁹ Heese et al⁴⁹ have reported decreasing protein concentrations in gloves manufactured using newer technology.

A correlation between glove wearing and the development of NRL allergy has been demonstrated in other studies:

- Heese et al²⁰ compared the prevalence of NRL allergy in a group of dental students at 2 time points 3 semesters apart. After the first time point, students regularly wore latex gloves. The prevalence of NRL allergy increased from 2% before glove use to 10.4% 3 semesters later.
- Brehler et al¹⁹ demonstrated that the use of powder-free gloves results in low rates of NRL sensitization. The finding of minimal NRL allergy in 2 English hospitals was attributed to the use of powder-free gloves with a low protein level, whereas the prevalence was much higher in a German hospital where only powdered gloves with high protein contents were worn.

Moreover, powder is an allergen carrier. The air in rooms where powdered NRL gloves are used has high concentrations of allergen,¹¹³ with much lower concentrations where powder-free gloves are used.^{114,115} Sensitized persons may have asthmatic and sys-

temic reactions to airborne NRL proteins associated with the use of powder. A hospital's changing from powdered, high-protein content gloves to powder-free or synthetic ones results in a decrease of airborne allergen levels to below the limit of detection within a few days.¹¹⁶ Strict avoidance of NRL products decreases the risk of latex allergy development even in identified risk groups. After construction of a special NRL-free operating room for children with spina bifida, none of 12 patients studied became sensitized to NRL allergens.¹¹⁷

Powdered gloves with a low protein content have become available in Germany, but a reduced risk for the development of NRL sensitization has not been demonstrated with the use of these gloves.

Prevention Guidelines

The primary prevention of NRL allergy is the avoidance of NRL exposure, but because of the ubiquity of NRL in products, this is nearly impossible. Threshold allergen exposure levels to avoid NRL sensitization are not defined. These levels may vary for individuals with atopic vs nonatopic predisposition. Natural rubber latex protein levels should be reduced to the lowest technically possible minimum. Individuals at high risk to develop sensitization should not be exposed to any NRL. These include children with congenital malformations and those with diseases bearing the risk of repeated surgical interventions. Persons who regularly wear gloves in their professions should use NRL-free gloves if eczema of the hand develops, especially if they have an atopic predisposition. Eczema lesions of the hand are opportunistic for the development of NRL sensitization by allowing protein to penetrate the skin. Less than 1% of NRL proteins penetrate intact skin, whereas 23% penetrate abraded skin.¹¹⁸

To identify patients who are sensitized to NRL, screening questionnaires may be used (**Table 3**). In sensitized individuals, NRL avoidance is the cardinal rule of NRL allergy control and to avoid life-threatening anaphylactic reactions.

Aerogen exposure from powdered gloves and other NRL products must be avoided. Contamination of foods with NRL allergens from kitchen personnel wearing powdered gloves can also lead to anaphylaxis.¹¹⁹ Finally, indirect contact with NRL proteins on surfaces contaminated with NRL, such as clothing,¹²⁰ can cause a life-threatening reaction.

Latex-safe environments for patients with NRL allergy should be provided in all medical and dental facilities. Medical procedures in high-risk patients should be performed in a latex-free setting. Substitute products without NRL are available for nearly all products containing NRL.

LEGISLATION

In 1997, a joint statement¹²¹ from the American Academy of Allergy, Asthma, and Immunology and the American College of Allergy, Asthma, and Immunology formulated new guidelines that only powder-free latex gloves should be purchased and used to reduce aeroallergen levels and exposure.

The Food and Drug Administration has begun requiring manufacturers to put allergy warnings on products or packaging containing latex and is regulating the mislabeling of these products as "hypoallergenic."¹²² Labels for NRL gloves must include the statement "Caution: This product contains natural rubber latex, which may cause allergic reactions."

In 1995, the American Society for Testing and Materials published standard test method D5712-95 for analyzing protein in natural rubber and NRL products. The Food and Drug Administration is proposing that the recommended limit on water-extractable protein per glove and the actual protein level appear on the label of NRL gloves. The proposed guidance document also recommends that manufacturers of NRL gloves used for surgery or examination limit the amount of water-extractable protein in the gloves to no more than 1200 µg of protein per glove, regardless of glove size. The lowest acceptable amount of water-extractable protein will be limited by the sensitivity of the current Ameri-

Table 3. Screening Questionnaires to Determine Latex Allergy in Children and Adults*

Children

Lip swelling, mucosal reactions, or asthma after blowing up balloons
History of atopic diseases

Adults

Contact urticaria rhinoconjunctivitis, asthma, or anaphylaxis after contact with NRL gloves, condoms, or other NRL products
Allergic reaction during medical or dental procedures or anaphylaxis during surgical interventions
Allergies to foods, with special regard to tropical fruits (banana, avocado, papaya, and chestnut)
History of hand eczema and atopic diseases

*NRL indicates natural rubber latex.

can Society for Testing and Materials D5712 test method to 50 µg of protein per gram of NRL product (300 µg of protein per glove for a 6-g glove). The Food and Drug Administration believes that without a more sensitive standard method lower claims would be misleading.

In Europe, no consensus exists for a recommendation to use powder-free gloves only. In Germany, guidelines for the use of NRL gloves were established by the Department of Labor and Social Affairs (Bundesministerium für Arbeit und Sozialordnung) in the Technical Regulations on Dangerous Substances (Technische Regeln für Gefahrstoffe, or TRGS) in December 1997. The TRGS describe the requirements for marketing and use of dangerous substances with regard to safety, occupational medicine, hygiene, and industrial science. TRGS 540 recommends replacing use of powdered NRL gloves with powder-free, low-allergen NRL ones or other suitable gloves. The protein level is required to be less than 30 µg per gram of glove. The standard test method is given in the European Standard EN 455-3 set by the European Committee for Standardization. However, the labeling of NRL protein concentrations on gloves is not required.

ECONOMICS

The issue of NRL allergy bears economic consequences. Addressing occupational latex allergy has direct costs, including the purchase of NRL-free and powder-free gloves, substitution of other hospital equipment, and the cost of installing

air filtration and laminar flow changing stations. The costs of implementing a dust-free and NRL-free working environment have been estimated at between \$75 000 and \$200 000 per year.¹²³ Indirect costs are worker-related and include job relocation to other areas in the hospital, job change with or without retraining, and additional education for other nonclinical employment.¹²³ It has been reported that in Canada the employer's cost will be more than Can \$200 000 for a registered nurse who has to stop work because of NRL allergy.¹²⁴ In Germany, the Employers Liability Insurance Association estimated costs of about \$83 000 for each individual with a legally ascertained occupational disease related to NRL allergy (Employers Liability Insurance Association, oral communication, 1997). At present, about 20% of occupational skin diseases and 33% of occupational asthma cases registered by the Berufsgenossenschaft für Gesundheitsdienst und Wohlfahrtspflege (the Employers Liability Insurance Association for many health care workers in Germany) are attributed to NRL allergy.

In a recent analysis of 3 health care institutions of different types, the costs of disability due to NRL allergy from continued latex use were compared with the costs of converting the facilities to be latex-safe. It was found that all facilities were likely to benefit economically from becoming latex-safe.¹²⁵

CONCLUSIONS

Because of the elasticity and durability of NRL, products containing

it are widely used at home and in professional occupations, especially in the medical field. For sensitized patients, it is essential to avoid any contact with NRL products. Use of the correct nomenclature and the labeling of NRL-containing products are essential. With current labeling, it is almost impossible to know for certain if a product is safe for patients allergic to NRL. Labeling of "latex" paint is misleading because paint does not contain NRL; here, the term *latex* is a technical description. At the other end of the spectrum, nonlabeling of NRL in glues, ampoule stoppers, and other products may pose an unexpected risk for sensitized patients.

Powder-free latex gloves usually contain lower protein levels than powdered latex gloves. For this reason and because of the potential hazards described herein, a legal ban on the use of powdered latex gloves is expected.

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Corresponding author and reprints: Randolph Brehler, MD, Department of Dermatology, Westfälische Wilhelms Universität, Von Esmerch Straße 56, 48149 Münster, Germany.

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